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(54) **Vaccine composition against *Streptococcus suis* infection**

(57) Described is a vaccine composition comprising an effective amount of at least one polypeptide or at least one vector selected from the group of

- (a) a protein designated ldeSsuis, an analogue or a fragment thereof,
- (b) a protein designated rldessuis, an analogue or a fragment thereof,
- (c) a vector with a polynucleotide inserted therein encoding the protein ldeSsuis, an analogue or a fragment thereof,
- (d) a vector with a polynucleotide inserted therein encoding the protein rldessuis, an analogue or a fragment thereof and

at least a pharmaceutical carrier, a diluent or an adjuvant.

Described is further a method for producing a protein rldessuis as a guest antigen in a vector or a different organism under condition suitable for expression of said recombinant protein.

Described herein is further the use of the vaccine composition, according to any of claims 1 to 11, to perform a prophylactic or metaphylactic or therapeutic treatment of a *Streptococcus suis* infection in pigs.

It has been shown that the vaccination of pigs using the protein rldessuis alone as the sole antigen provides a protection for pigs infected by *S. suis*

Description

[0001] The present invention relates to a vaccine composition and the use thereof for immunization and protection of mammals, in particular pigs, against *Streptococcus suis*.

[0002] *Streptococcus suis* (*S. suis*) colonizes the respiratory, alimentary and genital tract of pigs. *S. suis* is also one of the most important porcine pathogens, causing different pathologies such as meningitis, septicaemia, arthritis and endocarditis.

[0003] *S. suis* infections account for high production losses in the swine industry worldwide. Antibiotics are commonly used to treat *S. suis* infections. But recurrent infections frequently occur as well as the ongoing discussions concerning the reduction of antibiotic usage underline the need for alternative control measures. In Europe, no licensed vaccine is available but autologous bacterins are commonly used. A major drawback is the fact, that these vaccines protect only against the homologous serotype. But *S. suis* is a very diverse organism and different serotypes are responsible for morbidity in piglets. Especially serotype 2 strains play an important role for diseases in piglets worldwide.

[0004] *S. suis* serotype 2 has been identified to cause meningitis in adults in Asia, but to date no transmission of *S. suis* between humans has been detected.

[0005] In general infections elicit an early antigen-specific Immunoglobulin M (IgM) response leading to affinity maturation and isotope switching. Further, IgM antibodies present prior to infection, which are naturally occurring, are important in linking innate to adaptive immunity.

[0006] In pigs, IgM is especially important as monomeric membrane IgM (mIgM) as it is the only B-cell receptor occurring since IgD is missing in pigs. Further, IgM synthesis in newborn piglets starts much earlier than IgG and IgA synthesis. IgM in colostrum is crucial for the protection against pathogens which is carried out by complement-mediated killing. Therefore IgM antibodies are important in the protection against different pathogens.

[0007] Various virulence or virulence-associated factors of *S. suis* serotype 2 have been identified, among the capsule which is so far the only known essential virulence factor protecting the pathogen against phagocytosis. A number of surface-associated and secreted proteins of *S. suis* serotype 2 exhibit the same or very similar functions as homologous factors of other pathogenic streptococci. A variety of human or animal pathogens such as *Streptococcus pyogenes*, *Streptococcus equi* subspecies *equi* and *Streptococcus equi* subspecies *zooepidemicus* express specific IgG endopeptidases which are homologous to each other.

[0008] A surface-associated or secreted factor with a function unique for *S. suis* has been firstly described by Seele et al. ("Identification of a Novel Host-specific IgM Protease in *Streptococcus suis*." 2013; Journal of Bacteriology, 195: 930-940). Seele et al. showed that this IgM protease, designated IdeSsuis, does not function as an IgG endopeptidase. The IgM protease degrades opsonising IgM on the bacterial surface and therefore promotes the survival of *S. suis* in blood of bacterin-primed piglets. IdeSsuis is highly specific for IgM and does not cleave IgG or IgA.

[0009] The problem to be solved according to the invention is to overcome the problems described in the art and to provide a new vaccine composition to immunise and protect mammals, in particular pigs, against *S. suis* infections.

[0010] The problem is solved, according to the present invention, by providing a vaccine composition which comprises an effective amount of at least one polypeptide or at least one vector selected from the group of

- (a) a protein designated IdeSsuis, an analogue or a fragment thereof,
 - (b) a protein designated rIdeSsuis, an analogue or a fragment thereof,
 - (c) a vector with a polynucleotide inserted therein encoding the protein IdeS-suis, an analogue or a fragment thereof,
 - (d) a vector with a polynucleotide inserted therein encoding the protein rIdeS-suis, an analogue or a fragment thereof
- and

at least a pharmaceutical carrier, a diluent or an adjuvant.

[0011] The vaccine composition used in the present invention contains at least one sole polypeptide defined by (a) or (b) together with a pharmaceutical carrier or a diluent or an adjuvant or a mixture thereof. Further the vaccine may also comprise at least one sole vector defined by (c) or (d) with a pharmaceutical carrier, a diluent or an adjuvant or a mixture thereof.

[0012] Preferred is a vaccine composition, according to the present invention, wherein IdeSsuis of (a) comprises

- (a.a) the amino acid sequence of SEQ ID NO:1;
- (a.b) a fragment or an analogue of the amino acid sequence of SEQ ID NO:1; or
- (a.c) a fragment of either (a.a) or (a.b) having a IgM protease activity.

[0013] Further preferred is a vaccine composition, according to the present invention, wherein rIdeSsuis of (b) comprises

- (b.a) the amino acid sequence of SEQ ID NO:2;
(b.b) a fragment or an analogue of the amino acid sequence SEQ ID NO:2;
(b.c) an amino acid sequence lacking the amino acids from position 1 to 34 of the amino acid sequence SEQ ID NO:1;
(b.d) an amino acid sequence which is at least 60% homologue, preferably 70% homologue and most preferably 85% homologue to the amino acid sequence of the protein IdeSsuis of SEQ ID NO: 1; or
(b.e) a fragment of either (b.a) or (b.b) or (b.c) or (b.d) having a IgM protease activity.

[0014] Further preferred is a vaccine composition, according to the present invention wherein a fragment of the effective amount of said polypeptide of (a) or (b) is part of a fusion protein with at least one other protein.

[0015] Preferred is a vaccine composition, according to the present invention, wherein the polynucleotide of (c) comprises a sequence encoding a protein defined as IdeSsuis, namely

- (a.a) the amino acid sequence of SEQ ID NO:1;
(a.b) a fragment or an analogue of the amino acid sequence of SEQ ID NO:1; or
(a.c) a fragment of either (a.a) or (a.b) having a IgM protease activity.

[0016] Especially preferred is a vaccine composition, according to the present invention, which is characterized in that the polynucleotide comprises

- (c.a) a sequence of SEQ ID NO:3 or a complementary sequence thereto;
(c.b) a fragment of the sequence of (c.a) or
(c.c) a fragment of the sequence of (c.a) which encodes a protein having IgM protease activity.

[0017] Further preferred is a vaccine composition, according to the present invention, wherein the polynucleotide of (d) comprises a sequence encoding a protein defined as rIdeSsuis, namely

- (b.a) the amino acid sequence of SEQ ID NO:2;
(b.b) a fragment or an analogue of the amino acid sequence SEQ ID NO:2;
(b.c) an amino acid sequence lacking the amino acids from position 1 to 34 of the amino acid sequence SEQ ID NO:1;
(b.d) an amino acid sequence which is at least 60% homologue, preferably 70% homologue and most preferably 85% homologue to the amino acid sequence of the protein IdeSsuis of SEQ ID NO: 1; or
(b.e) a fragment of either (b.a) or (b.b) or (b.c) or (b.d) having a IgM protease activity.

[0018] Especially preferred is a vaccine composition, according to the present invention, which is characterized in that the polynucleotide comprises

- (d.a) a sequence of SEQ ID NO:4 or a complementary sequence thereto;
(d.b) a fragment of the sequence of (d.a) or
(d.c) a fragment of the sequence of (d.a) which encodes a protein having IgM protease activity

[0019] Preferred is a vaccine composition, according to the present invention, wherein the polynucleotide is DNA or RNA.

[0020] Further it is preferred that a vaccine composition, according to the present invention, is further characterized by the polynucleotide integrated into a vector, wherein the polynucleotide is operable linked to an expression control region of the vector, wherein the vector is an expression vector which is a plasmid or a viral vector.

[0021] It is also preferred that a vaccine composition, according to the present invention, is provided in a physiologically administrable form and is suitable for intramuscular, intravenous, subcutaneous or dermal injection or mucosal application.

[0022] Another object of the present invention is a host cell which is transfected with the vector.

[0023] A further object of the present invention is a method for producing a protein defined as rIdeSsuis as a guest antigen in a vector or a different organism, respectively a host cell transfected under condition suitable for expression of said recombinant protein.

[0024] Another object of the present invention is the use of the vaccine composition, according to the present invention, to perform a prophylactic or metaphylactic or therapeutic treatment of a *Streptococcus suis* infection in pigs.

[0025] Especially preferred is the use of the vaccine composition, according to the present invention, wherein the treatment causes an immunological response in pigs whereas the immunological response is the activation of a humoral and cellular response against the protein IdeSsuis produced by *Streptococcus suis*.

[0026] The present invention is further described with the following figures, where

Fig. 1 shows a time table representing the vaccination challenge experiments with *S. suis* in pigs and

Fig. 2 shows a graph representing the results gained with the vaccination challenge experiments of Fig. 1.

5 Attached is a Sequence listing.

[0027] SEQ ID NO 1 shows the amino acid sequence of the protein IdeSsuis;

[0028] SEQ ID NO 2 shows the amino acid sequence of the recombinant protein rIdeSsuis without the signal peptide;

[0029] SEQ ID NO 3 shows the nucleotide sequence of the gene *IdeSsuis* and

10 [0030] SEQ ID NO 4 shows the nucleotide sequence of the gene *rIdeSsuis*.

[0031] The preparation of the vaccine composition according to the invention is known in the art, and is described in handbooks known to the person skilled in the art.

[0032] Thus, the present invention is directed to a vaccine composition comprising a protein designated as IdeSsuis or rIdeSsuis or a fragment of either thereof; or a polynucleotide either expressing the protein IdeSsuis or rIdeSsuis or a fragment either thereof which is integrated into an expression vector, whereas the recombinant protein is preferred.

15 [0033] The inventors detected the following:

(a) the induction of opsonising antibodies is crucial for the protective efficacy of a *S. suis* bacterin.

(b) IdeSsuis promotes survival of *S. suis* in blood of vaccinated piglets.

20 [0034] Further the inventors showed, that the vaccination of pigs using the protein rIdeSsuis alone **as the sole antigen** provides a protection for pigs infected by *S. suis*. According to the invention vaccination with rIdeSsuis prevents the cleavage of IgMs by the IdeSsuis IgM protease of *S. suis* by inducing neutralizing antibodies.

[0035] According to the invention, the vaccination of pigs with the recombinant protein rIdeSsuis or a fragment thereof led to high titers of IdeSsuis-specific IgG antibodies with neutralizing activity in contrast to reconvalescent or *S. suis* bacterin immunized piglets.

25 [0036] Further the inventors showed, that the vaccination of pigs with the recombinant protein rIdeSsuis or a fragment thereof reduces the survival of *S. suis* in the blood

[0037] For the production of the vaccine composition according to the present invention pharmaceutically acceptable carriers, diluents or adjuvants which can be used which comprise but are not limited to the following: mineral salt adjuvants

30 (e.g., alum-, calcium-, iron-, zirconium-based), tensoactive adjuvants (e.g., Quil A, QS-21, other saponins), bacteria-derived adjuvants (e.g., N-acetyl muramyl-L-alanyl-D-isoglutamine (MDP), lipopolysaccharides (LPS), monophosphoryl lipid A, trehalose dimycolate (TDM), DNA, CpGs, bacterial toxins), adjuvant emulsions (e.g., FIA, Montanide, Adjuvant 65, Lipovant), liposome adjuvants, polymeric adjuvants and carriers, cytokines (e.g., Granulocyte-macrophage colony stimulating factor), carbohydrate adjuvants, living antigen delivery systems (e.g., bacteria, viruses).

35 Furthermore carriers can also comprise dry formulations such as coated patches made from titan or polymer.

[0038] Further, according to the present invention, the proteins IdeSsuis or rIdeSsuis or fragments thereof can also be used in fusion proteins. Fusion proteins are created by joining two or more genes which are originally coded for separate proteins. The translation of this fusion gene results in a single or multiple polypeptide with functions derived each from the originally proteins.

In the state of the art, fusion proteins are often used to simplify specific applications, such as detection, integration or transport of the protein of interest. A prominent member for detection by fluorescent microscopy is the green fluorescent protein (GFP) fused to the protein of interest.

[0039] Other proteins which could be fused to IdeSsuis to improve the delivery and immunogenicity of the antigen are immunoglobulin FC-fragment, non-toxic cholera toxin CTA subunit, mutated heat-labile toxins, *Bacillus subtilis* spore coat protein or bacterial flagellins. Furthermore fusionproteins with proteins of viruses or phages (e.g. modified vaccinia virus Ankara (MVA), Hepatitis B virus, Lambda phage or filamentous bacteriophages like fd, M13 or fl) can be used for the expression of IdeSsuis on the surface of a virus particle or a virus-like particle.

40 [0040] Another possibility to detect fusion proteins is the usage of so called protein tags which are often used during the production of fusion proteins respectively their purification and detection by performing affinity chromatography, western blotting, immunohistochemistry or fluorescent microscopy. Protein tags are commonly short amino acid sequences for example HIS-Tag, myc-Tag, HA-Tag, Step-Tag, GST-Tag, maltose binding protein-Tag or Thioredoxin-Tag.

[0041] The method for producing recombinant proteins such as rIdeSsuis according to the present invention is known by the person skilled in the art and also described by handbooks known by the person skilled in the art.

55 In general host cells are used for being transfected with a vector encoding the protein of interest for production of a recombinant protein. In general those host cells may be bacteria (e.g. *E.coli*, *Bacillus* or *Lactococcus* strains), human (e.g. 293-T, HEK-293), mouse cell lines, insect cell lines, yeast cells or plant based systems.

[0042] For the transfection of host cells expression vectors such as plasmids (e.g. pET, pQE), viruses and phages

(e.g. baculovirus, Lambda phage or filamentous bacteriophages) can be used.

[0043] Typically such vaccine compositions are prepared as injectables, either as liquid solutions or suspensions.

[0044] The subject of the present invention is also a vaccine composition for subcutaneous, intravenous, intramuscular, dermal or mucosal application.

5 **[0045]** The following examples shall explain the present invention. The examples shall be understood only as one preferred embodiment of the invention. It is not intended to limit the present invention to the scope of the given examples.

[0046] The following examples provide experimental data after performing vaccination challenge experiments in piglets infected by *S. suis*.

10 **Example 1**

[0047] Establishment of vaccination challenge experiments in piglets for different *S. suis* serotypes (serotype 2 and 9) and infection routes (intravenous and intranasal).

15 **[0048]** Briefly as shown in Fig. 1, piglets at an age of three to four weeks were prime vaccinated with a rIdESsuis vaccine. At an age of 5 to 6 weeks these piglets were boosted with rIdESsuis and in one group also prime vaccinated with a bacterin by intramuscular injection (given in the table in Fig. 1). The piglets were challenged two weeks after the second immunizations intranasally. Animals were further monitored every eight hours. For reasons of animal welfare, animals were euthanized in any case in which a piglet exhibits high fever in combination with apathy and anorexia as well as in the case of clinical signs of acute polyarthritis or severe meningitis.

20 **[0049]** All surviving piglets were sacrificed at 14 days post infection.

[0050] The experiment revealed that the immunization of piglets by using the recombinant protein rIdESsuis by itself is enough to protect piglets from infections by *S. suis* serotype 2 (Fig. 2).

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EP 2 949 340 A1

SEQUENCE LISTING

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EP 2 949 340 A1

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EP 2 949 340 A1

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EP 2 949 340 A1

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EP 2 949 340 A1

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EP 2 949 340 A1

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EP 2 949 340 A1

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EP 2 949 340 A1

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Claims

- 20 1. A vaccine composition comprising an effective amount of at least one polypeptide or at least one vector selected from the group of
- (a) a protein designated IdeSsuis, an analogue or a fragment thereof,
 - (b) a protein designated rIdeSsuis, an analogue or a fragment thereof,
 - 25 (c) a vector with a polynucleotide inserted therein encoding the protein IdeSsuis, an analogue or a fragment thereof,
 - (d) a vector with a polynucleotide inserted therein encoding the protein rIdeSsuis, an analogue or a fragment thereof and
 - at least a pharmaceutical carrier, a diluent or an adjuvant.
- 30 2. The vaccine composition, according to claim 1, **characterized in that** IdeSsuis of (a) comprises
- (a.a) the amino acid sequence of SEQ ID NO:1;
 - (a.b) a fragment or an analogue of the amino acid sequence of SEQ ID NO:1; or
 - 35 (a.c) a fragment of either (a.a) or (a.b) having a IgM protease activity.
3. The vaccine composition, according to claim 1, **characterized in that** rIdeSsuis of (b) comprises
- (b.a) the amino acid sequence of SEQ ID NO:2;
 - 40 (b.b) a fragment or an analogue of the amino acid sequence SEQ ID NO:2;
 - (b.c) an amino acid sequence lacking the amino acids from position 1 to 34 of the amino acid sequence SEQ ID NO:1;
 - (b.d) an amino acid sequence which is at least 60% homologue, preferably 70% homologue and most preferably 85% homologue to the amino acid sequence of the protein IdeSsuis of SEQ ID NO: 1; or
 - 45 (b.e) an fragment of either (b.a) or (b.b) or (b.c) or (b.d) having a IgM protease activity.
4. The vaccine composition, according to at least one of claim 1 to 3, **characterized in that** a fragment of the effective amount of said polypeptide of (a) or (b) is part of a fusion protein with at least one other protein.
- 50 5. The vaccine composition, according to claim 1, **characterized in that** said polynucleotide of (c) comprises a sequence encoding a protein as defined in claim 2.
6. The vaccine composition, according to claim 5, **characterized in that** said polynucleotide comprises
- 55 (c.a) a sequence of SEQ ID NO:3 or a complementary sequence thereto;
 - (c.b) a fragment of the sequence of (c.a) or
 - (c.c) a fragment of the sequence of (c.a) which encodes a protein having IgM protease activity.

EP 2 949 340 A1

7. The vaccine composition, according to claim 1, **characterized in that** said polynucleotide of (d) comprises a sequence encoding a protein as defined in claim 3.

8. The vaccine composition, according to claim 7, **characterized in that** said polynucleotide comprises

(d.a) a sequence of SEQ ID NO:4 or a complementary sequence thereto;

(d.b) a fragment of the sequence of (d.a) or

(d.c) a fragment of the sequence of (d.a) which encodes a protein having IgM protease activity

9. The vaccine composition, according to at least one of claim 5 to 8, **characterized in that** said polynucleotide is DNA or RNA.

10. The vaccine composition, according to at least one of claim 5 to 9, **characterized in that** said polynucleotide is integrated into a vector, wherein the polynucleotide is operable linked to an expression control region of the vector, wherein the vector is an expression vector which is a plasmid or a viral vector.

11. The vaccine composition, according to any of the previous claims, **characterized in that** it is provided in a physiologically administrable form and is suitable for intramuscular, intravenous, subcutaneous or dermal injection or mucosal application.

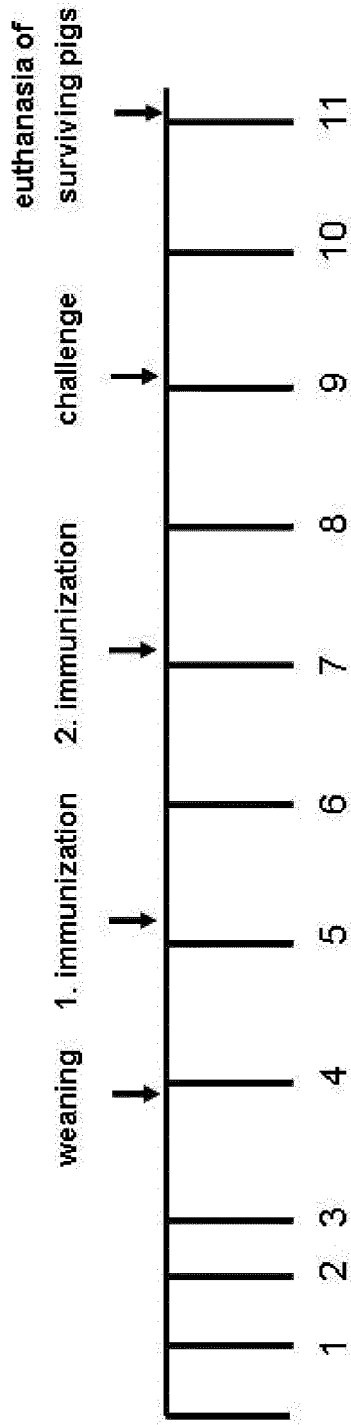
12. A host cell transfected with the vector according to claim 10.

13. A method for producing a protein rIdeSsuis as a guest antigen in a vector or a different organism according to claim 12 under condition suitable for expression of said recombinant protein.

14. Use of the vaccine composition, according to any of claims 1 to 11, to perform a prophylactic or metaphylactic or therapeutic treatment of a *Streptococcus suis* infection in pigs.

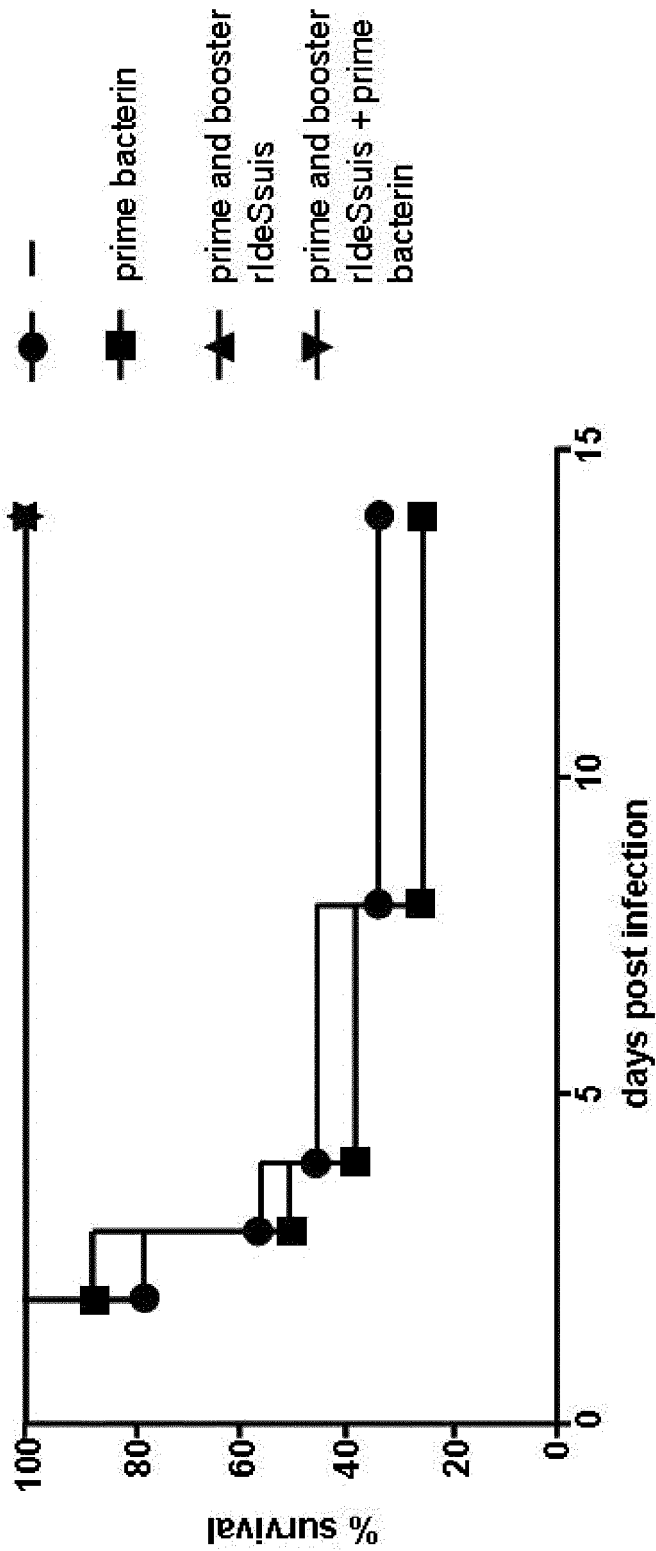
15. Use of the vaccine composition, according to claim 14, **characterized in that** the treatment causes an immunological response in pigs whereas the immunological response is the activation of a humoral and cellular response against the protein IdeSsuis produced by *Streptococcus suis*.

Fig. 1



number of pigs	1. immunization	2. immunization	challenge
9	rIdeSsuis (0.4mg/piglet)	rIdeSsuis (0.25mg/piglet) + bacterin (S. suis serotype 2 strain 19841)	S. suis serotype 2 strain 10
9	rIdeSsuis (0.4mg/piglet)	rIdeSsuis (0.25mg/piglet)	S. suis serotype 2 strain 10
8	placebo	bacterin (S. suis serotype 2 strain 19841)	S. suis serotype 2 strain 10
9	placebo	placebo	S. suis serotype 2 strain 10

Fig. 2



-vs. prime bacterin : $p= 0.8237$
 -vs. prime and booster rIdeSsuis: $p= 0.0031$
 -vs. prime and booster rIdeSsuis + prime bacterin: $p= 0.0031$
 prime bacterin vs. prime and booster rIdeSsuis: $p=0.0013$
 prime bacterin vs. prime and booster rIdeSsuis + prime bacterin: $p= 0.0013$



EUROPEAN SEARCH REPORT

Application Number
EP 14 17 0637

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Y	* p.930, right col., p.933, right col.; figure 3 * -& SEELE JANA ET AL: "Online Supplemental material (Identification of a novel host-specific IgM protease in Streptococcus suis).", JOURNAL OF BACTERIOLOGY, vol. 195, no. 5, May 2013 (2013-05), page 17PP, XP002730290, ISSN: 1098-5530 * the whole document *	1-11,14,15	TECHNICAL FIELDS SEARCHED (IPC) A61K C12N
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3 The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 18 September 2014	Examiner Heder, Andreas
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

EPO FORM 1503 03.82 (F04C01)



EUROPEAN SEARCH REPORT

Application Number
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X	----- WO 2004/020618 A1 (IMPFFSTOFFWERK DESSAU TORNAU GM [DE]; GOETHE RALPH [DE]; VALENTIN-WEIGA) 11 March 2004 (2004-03-11)	1-4,6,7, 11	TECHNICAL FIELDS SEARCHED (IPC)
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Place of search Munich		Date of completion of the search 18 September 2014	Examiner Heder, Andreas
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**ANNEX TO THE EUROPEAN SEARCH REPORT
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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